[0016H] on p.59 of the spec.

Please replace paragraph number ~~[0164]~~ with the following rewritten paragraph:

[0001] [0164] Lyophilized particles were prepared from tris buffer solutions (5 or 50 mM: pH 7.6) containing hGH (5 mg/mL) using a Durastop μP Lyophilizer in accordance with the following freezing and drying cycles:

Freezing cycle	Ramp down at ~~2.5~~ 2.5° C~~C~~/min to -30° C to and hold for 30 min
	Ramp down at ~~2.5 C~~ 2.5° C/min to -30° C and hold for 30 min
Drying cycle	Ramp up at ~~0.5 C~~ 0.5° C/min to 10° C and hold for 960 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 20° C and hold for 480 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 25° C and hold for 300 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 30° C and hold for 300 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 5° C and hold for ~~5000~~ 5,000 min

Please replace paragraph number **[0165]** with the following rewritten paragraph:

Example 3

~~HGH~~hGH-Stearic Acid Particle Preparation

[0165] Human growth hormone (hGH) particles were prepared as follows: Lyophilized hGH (3.22 grams, Pharmacia-Upjohn, Stockholm, Sweden) and stearic acid (3.22 grams, 95% pure, Sigma-Aldrich Corporation, St. Louis, MO) were blended and ground. The ground material was compressed in a 13 mm round die, with a force of 10,000 pounds for 5 minutes. Compressed tablets were ground and sieved through a 70 mesh screen followed by a 400 mesh screen to obtain particles having a size range between 38 - 212 microns.

[000159] starting on p. 59 of the spec.

Please replace paragraph number ~~[0166]~~ with the following rewritten paragraph:

Example 4

Bupivacaine base Preparation

[0166] Bupivacaine hydrochloride (Sigma-Aldrich Corporation, St. Louis, MO) was dissolved in ~~de-~~deionized (DI) water at a concentration of 40 mg/ml (saturation). A calculated amount of sodium hydroxide (in the form of 1 N solution) was added to the solution and the pH of the final mixtures was adjusted to 10 to precipitate the Bupivacaine base. The precipitated product was filtered, and further washed with DI water ~~for at~~ at least three times. The precipitated product was dried at ca. 40° C in vacuum for 24 ~~h~~ hours.

[000160] on p. 60 of the spec.

Please replace paragraph number ~~[0167]~~ with the following rewritten paragraph:

Example 5

Bupivacaine Particle Preparation

[0167] Bupivacaine drug particles (both base and hydrochloride salt) were prepared as follows. Bupivacaine hydrochloride (Sigma-Aldrich Corporation, St. Louis, MO) or bupivacaine base prepared ~~according~~ according to Example 4 were grounded and then sieved to a fixed range using 3" stainless steel sieves. Typical ranges include 25μm to 38μm, 38μm to 63μm, and 63μm to 125μm.

[000162] on p. 60 of the spec.

Please replace paragraph number ~~[0169]~~ with the following rewritten paragraph:

Example 7

Preparation of Leuprolide Acetate Particles

[0169] Leuprolide acetate (Mallinckrodt Inc., St. Louis, ~~MI~~ MO) was ground and sieved between ~~63-125 μm~~ 63-125μm sieves (for nominal particle size of ~~90 μm~~ 90μm). An GILSON digital Sieve Shaker may be employed to speed the sieving (Gilson Company Inc., Worthington, OH).

[000163] on p.61 of the spec.

Please replace paragraph number ~~[0170]~~ with the following rewritten paragraph:

Example 8

Preparation of Leuprolide Acetate-Stearic Acid Particles

[0170] Stearic acid (95% pure, Sigma-Aldrich Corporation, St. Louis, MO) was passed through a 120-mesh screen (~~125 μm~~125μm). Equal amounts of milled leuprolide acetate (~~<63 μm~~<63μm, prepared as described in Example 2 above) and sieved stearic acid were transferred to the Waring blender and blended for 30 seconds. The blended materials were compressed in a 13 mm round die ~~using~~ using a compression force of ~~5000~~ 5,000 lbs and hold time of 5 min. Compressed pellets were ground and sieved through a 120-mesh (~~125 μm~~125μm) sieve and retained on a 230 mesh (~~63 μm~~63μm) sieve.

[000164] on p.61 of the spec.

Please replace paragraph number ~~[0171]~~ with the following rewritten paragraph:

Example 9

Preparation of Buprenorphine Particles

[0171] Buprenorphine hydrochloride (100 grams, Sigma-Aldrich Corporation, St. Louis, MO) was ground and sieved through ~~pre-~~preselected sieves such as 25, 38, 62 or 125 micron sieves depending on the desirable particle sizes to obtain the corresponding Buprenorphine particles.

[000165] on p.61 of the spec.

Please replace paragraph number ~~[0172]~~ with the following rewritten paragraph:

Example 10

Preparation of Buprenorphine-Stearic Acid Particles

[0172] Equal ~~amount~~ amounts of Buprenorphine particles (prepared as described in Example ~~4) above~~ above) and stearic acid (prepared as described in Example 3) were blended and ground. The ground material was compressed in a 13 mm round die, with a force of 5,000 pounds for 5 minutes. Compressed tablets were ground and sieved through a 120 mesh screen followed by a 230 mesh screen to obtain particles having a size range between 63-125 microns.

[00016] starting on p.63 of the spec.

Please replace paragraph number ~~[0174]~~ with the following rewritten paragraph:

[0174]

Table 4

Formulation	PLGA RG502[4a] (wt%)	LMW PLGA (wt%)	Benzyl Benzoate (wt%)
17[4c]	45	0[4b]	45
18[4c]	0	45[4b]	45
19[4d]	45	0[4b]	45
20[4d]	0	45[4b]	45
21[4f]	45	0[4e]	45
22[4f]	0	45[4e]	45
23[4f]	0	63[4e]	27

4a = PLGA RG 502, MW = 16,000.
4b = Low Molecular Weight (LMW, MW = ~~8000~~ 8,000) PLGA with an ester end group.
4c = 10% bupivacaine hydrochloride loading.
4d = 10% bupivacaine base loading.
4e = Low Molecular Weight (LMW, MW - 7,000) PLGA with an ester end group
4f = 5% hGH loading.

Table 5

Formulation	LMW PLGA[5g] (wt%)	LMW PLGAc[5h] (wt%)	Benzyl Benzoate (wt%)	Benzyl Alcohol (wt%)
24[5i]	58.5	0	31.5	0
25[5i]	58.5	0	0	31.5
26[5i]	67.5	0	0	22.5
27[5i]	0	67.5		22.5
28[5j]	0	60		20

5g = Low Molecular Weight (LMW, MW = 8,000) PLGA with an ester end group.
5h = Low Molecular Weight (LMW, MW = 10,000) PLGA with a carboxyl end group.
5i = 10% bupivacaine hydrochloride loading.
5j = 10% bupivacaine hydrochloride and 10% SA loading.

Table 12

Formulation	P(DL)LA R202 (wt%)	BB (wt%)	BA (wt%)
58[12a,b]	50.6	41.4	-
59[12a,b]	50.6	-	41.4
60[12b,c]	55.0	45.0	-
61[12b,c]	55.0	-	45.0

12a = ~~8 wt%~~ 8 wt.% leuprolide acetate loaded;
12b = 100 mg depot injection per rat;
12c = Placebos without leuprolide acetate.

[000168] on p.66 of the spec.

Please replace paragraph number ~~[0175]~~ with the following rewritten paragraph:

Example 12

Rheological Properties ~~Of~~ of Depot Formulations

[0175] In general, viscosity of the depot vehicle formulations was tested using a Bohlin CVO 120 rheometer (Bohlin Instruments, Cranbury, NJ). All testing ~~were~~ was performed at 24° C using 20 mm parallel plates. The viscosity of various gel formulations or leuprolide acetate depot formulations of the invention, as tabulated in Tables 6-12, was tested as described above. As illustrated in Figures 1, 2 and ~~3~~ 3, the depot formulations (Formulations # 42-48, 51 and 52) have different rheological properties. Thus, the depot formulations ~~with~~ with a wide range of viscosities can be achieved by the combination of different polymers (PLGA type, molecular weight etc.), solvent or co-solvent, and different polymer/solvent ratios according to the present invention.

[000169] on p.66 of the spec.

Please replace paragraph number ~~[0176]~~ with the following rewritten paragraph:

Example 13

Injection force of leuprolide acetate depot formulations

[0176] The injection force of the depot vehicle formulations was tested on an Instron tensile testing instrument (Instron, Canton, MA), where the maximum force required to move the syringe plunger at a speed of 1 ml/minute was determined. The vehicle formulations were ~~pre-~~prefilled into Hamilton syringes prior to the Instron tests. All tests were conducted at room temperature, using a 24-gauge 0.5 inch long needle.

[0001 70] on p.66 of the spec.

Please replace paragraph number ~~[0177]~~ with the following rewritten paragraph:

[0177] The injection force of various gel formulations or leuprolide acetate depot formulations of the invention, as tabulated in Tables 6-12, was tested as described above. As illustrated in Figures 4 and 5, the depot formulations (Formulations 42-45 and 48-50) have different injection forces. Thus, depot formulations with different injection forces can be tailored by the combination of different polymers (PLGA type, molecular weight etc.), solvent or co-solvent, ~~different~~ or different polymer/solvent ratios according to the present invention.

[0001 70] on p.67 of the spec.

Please replace paragraph number ~~[0178]~~ with the following rewritten paragraph:

Example 14

In Vitro Release Rate Profiles of Depot Gel Formulations

[0178] A representative number of implantable gels were prepared in accordance with the foregoing procedures and tested for *in vitro* release of beneficial agent as a function of time. In general, the *in vitro* release of bioactive agent from the depot formulation of the present invention was performed as follows. The depot gel formulation (80-120 mg) was loaded into a tea bag and placed in a 20 mL scintillation vial and the release medium (5 mL, phosphate buffer saline (PBS) + 0.1% Tween 20, pH 7.4) was added to the vial. The vial was incubated in a 37° C water bath with gentle agitation. The medium was replaced daily for the first 5 days, then twice a week thereafter ~~till~~ until the end ~~of~~ of the release duration. The amount of bioactive agent released from the depot was measured by various methods dependent ~~the~~ on the nature of the bioactive agent: size exclusion chromatography high pressure liquid chromatography (SEC HPLC) is generally used for protein, while reverse phase high pressure liquid chromatography (rpHPLC) or ultraviolet (UV) techniques are generally used for small molecular compounds.

[00072] starting on p.67 of the spec.

Please replace paragraph number ~~[0180]~~ with the following rewritten paragraph:

[0180] In general, *in vivo* studies in rats were performed following an open protocol to determine plasma levels of the beneficial agent (e.g., hGH, bupivicaine, leuprolide, buprenorphine) upon systemic administration of the beneficial agent via the implant systems of this invention. Depot gel formulations containing the beneficial agent (prepared as described in the Examples above) were loaded into 0.25 cc ~~or a~~ or 0.5 cc disposable syringes (~~e.g.~~e.g., Hamilton Gastight syringes) or catheters. Disposable needles (16 gauge or 18 gauge) were attached to the syringes and were heated to 37° C using a circulator bath. The depot gel formulations (as tabulated in Tables 1-12) were injected into rats and blood was drawn at specified time intervals. All plasma samples were stored at 4° C prior to analysis. Samples were analyzed for the beneficial agent using any one of the following methods: radio immuno assay (RIA) or validated LC/MS/MS method (Ricerca, LLC, Painesville, Ohio).

[00073] on p.68 of the spec.

Please replace paragraph number ~~[0181]~~ with the following rewritten paragraph:

Example 16

hGH *In Vivo* Studies

[0181] A representative number of implantable gels as tabulated in Tables 4-6 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, depot gel hGH compositions were injected from customized 0.5 cc disposable syringes having disposable 16 gauge needles, into rats and blood was drawn at specified time intervals. The release rate profile of hGH from various depot gel formulations was determined by measuring the blood serum or plasma concentrations of hGH as a function of time, as illustrated in ~~Figure~~ Figures ~~6~~ 6A-D (formulations 21, 22, 29-31, and 33-40). Samples were analyzed for intact hGH content using a radio immuno assay (RIA).

[0017 4] starting on p. 68 of the spec.

Please replace paragraph number ~~[0182]~~ with the following rewritten paragraph:

Example 17

Bupivacaine *In Vivo* Studies

[0182] A representative number of implantable gels as tabulated in Table 4 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, depot gel bupivacaine compositions were injected from customized 0.5 cc disposable syringes having disposable 18 gauge needles, into rats and blood was drawn at specified time intervals (1 hour, 4 hours and on days 1, 2, 5, 7, 9 and 14, 21 and 28) and analyzed for bupivacaine using LC/MS. Figures 7, 8 and 9 illustrate representative *in vivo* release profiles of bupivacaine hydrochloride (formulations 17 and 18) and bupivacaine base (formulations 19 and 20) obtained in rats from various depot ~~formulation,~~ formulations, including those of the present invention. The *in vivo* release profile of the depot formulations with low molecular weight PLGA (formulations 18 and 20 in Figures 7, 8 and 9) exhibited a shorter release duration of approximately 7 days, as compared to the control formulations (with higher molecular weight PLGA, formulations 17 and 19).

[0017 5] on p. 69 of the spec.

Please replace paragraph number ~~[0183]~~ with the following rewritten paragraph:

Example 18

Bupivacaine *In Vivo* Studies

[0183] A representative number of implantable gels as tabulated in Table 13 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 17 above. Figures 10 and 11 illustrate representative *in vivo* release profiles of bupivacaine obtained in rats from various depot ~~formulation,~~ formulations, including those of the present invention. As illustrated in the figures, when the same amount of bupivacaine was administrated, the duration of the *in vivo* sustained release of bupivicaine from the formulation is directly proportional to the percent loading of bupivacaine within the depot gel composition. In particular, at 10% bupivicaine HCl loading, the amount of bupivicaine released increased with time after an initial decline during the first two weeks. Although not wanting to be limited to a particular theory, the

results indicate that the early stage diffusion mechanism may be the primary mechanism contributing to the release of the beneficial agent, while at later stages, polymer degradation might significantly contribute to the release.

Table 13

Formulation	PLGA RG502 (wt%)	Benzyl Benzoate (wt%)	Bupivacaine (wt%)
62	35	35	30[13a]
63	45	45	10[13a]
64	35	35	30[13b]
65	45	45	10[13b]

a = particle size of bupivacaine is ca. ~~35 µm~~ 35µm;
b = particle size of bupivacaine is ca. ~~90 µm~~ 90µm.

[0077] on p. 70 of the spec.

Please replace paragraph number ~~[0184]~~ with the following rewritten paragraph:

Example 19

In Vivo Studies on Bupivacaine Depot Composition With Different PLGA Molecular Weight Distributions

[0184] A representative number of implantable gels as tabulated in Table 2 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, depot gel bupivacaine compositions were injected from customized 0.5 cc disposable syringes having disposable ~~18~~ 18-gauge needles, into rats and blood was drawn at specified time intervals (1 hour, 4 hours and on days 1, 2, 5, 7, 9 and 14, 21 and 28) and analyzed for bupivacaine using LC/MS. Figure 12 illustrates the representative *in vivo* release profiles of bupivacaine obtained in rats from the formulations 11 and 12 (the bupivacaine depots were formulated with the PLGAs with two different molecular weight distributions in benzyl benzoate (single-modal containing MMW PLGA RG502, and bi-modal mixture of HMW PLGA RG503 with LMW PLGA, Table 2 formulations 11 and 12).

[00017] on p. 70 of the spec.

Please replace paragraph number ~~[0185]~~ with the following rewritten paragraph:

Example 20

In Vivo Release Rate Profiles of

Various Leuprolide Acetate Depot Formulations

[0185] A representative number of implantable gels as tabulated in Tables 7-9 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, ~~release~~ the release rate profile of leuprolide was determined by measuring the blood serum or plasma concentrations of leuprolide as a function of time, as illustrated in Figures 13-16.

[00018] starting on p. 70 of the spec.

Please replace paragraph number ~~[0186]~~ with the following rewritten paragraph:

[0186] In particular, Figure 13 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in either benzyl benzoate (BB) (~~formulation42~~formulation 42) or benzyl alcohol (BA) (formulation 47), as compared to a commercial 3-month leuprolide acetate depot, Lupron depot® (formulation 53). Figure 14 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in benzyl benzoate, ~~mixture~~ a mixture of benzyl benzoate and benzyl alcohol, or benzyl benzoate with ethanol as a thixotropic agent (formulations 42, 43 and 45, respectively). Figure 15 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in benzyl benzoate with the drug particles formulated either with or without stearic acid (formulations 42 & 49). Figure 16 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing poly(caprolactone-co-lactic acid) (PCL-co-LA) (CL/L : 25/75) in benzyl benzoate (formulation 46) as compared to a commercial 3-month leuprolide acetate depot, Lupron depot® (formulation 53 - from TAP (The front chamber of Lupron depot® ~~3 month~~ 3-month 11.25 mg prefilled dual-chamber syringe containing leuprolide acetate (11.25 mg),

polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP and glacial acetic acid, USP to control pH.)).

[000180] Starting on p. 71 of the spec.

Please replace paragraph number ~~[0188]~~ with the following rewritten paragraph:

Example 21

In Vivo Release Rate Profiles of

Various Leuprolide Acetate Depot Formulations

[0188] A representative number of implantable gels as tabulated in Table 10 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, ~~release~~ the release rate profile of leuprolide was determined by measuring the blood serum or plasma concentrations of leuprolide as a function of time, as illustrated in Figure 17.

[000181] on p. 72 of the spec.

Please replace paragraph number ~~[0189]~~ with the following rewritten paragraph:

[0189] In particular, Figure 17 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing P(DL)LA in benzyl benzoate (BB) with different polymer/solvent ratios (~~formulation~~formulations 51 and 52), as compared to the 3 month durational depot formulation (formulation 42) and a commercial 3-month leuprolide acetate depot, Lupron depot® (formulation 53).

[000182] on p. 72 of the spec.

Please replace paragraph number ~~[0190]~~ with the following rewritten paragraph:

[0190] As illustrated in Figure 17, sustained release of leuprolide acetate from the ~~depots formulation~~ depot formulations of the invention can be achieved for a duration greater than or equal to 6 months by using the biodegradable polymer with longer degradation duration. The release profiles of the active agent from the depots can be varied by varying the type of polymer and solvent, and by varying the polymer/solvent ratios.

[0000183] on p.72 of the spec.

Please replace paragraph number ~~[0191]~~ with the following rewritten paragraph:

Example 22

InVivo Release Rate Profiles of Various ~~BuprEnorphine~~ Buprenorphine Depot Formulations

[0191] A representative number of implantable buprenorphine depot gel formulations of the present invention are tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, ~~release~~ the release rate profile of buprenorphine is determined by measuring the blood serum or plasma concentrations of leuprolide as a function of time. The release profiles of the active agent from the depots can be varied by varying the type of polymer and solvent, and by varying the polymer/solvent ratios.

[0000184] on p.73 of the spec.

Please replace paragraph number ~~[0192]~~ with the following rewritten paragraph:

Example 23

In Vivo Testosterone Suppression by Depot Gel Leuprolide Formulations

[0192] In general, *in vivo* studies in rats were performed following an open protocol to determine plasma levels of leuprolide upon systemic administration of leuprolide via the implant systems of this invention. Depot gel leuprolide formulations (prepared as described in Examples above) were loaded into 0.25 cc Hamilton Gastight syringes. Disposable ~~18~~ 18-gauge needles were attached to the syringes and were heated to 37° C using a circulator bath. Depot gel leuprolide acetate formulations were injected into rats and blood was drawn at specified time intervals. All plasma samples were stored at 4° C prior to analysis. Samples were analyzed for leuprolide as described in Example 15 above, and for testosterone using a commercially available RIA kit (DSL-4000) (Ricerca, LLC, Painesville, Ohio).

[00185] on p. 73 of the spec.

Please replace paragraph number ~~[0193]~~ with the following rewritten paragraph:

Example 24

~~*InVivo*~~*In Vivo* Release Rate Profiles and Efficacy of

Various Leuprolide Acetate Depot Formulations

[0193] A representative number of implantable gels as tabulated in Table 11 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles and efficacy as measured by testosterone suppression as described in Example 23 above. In particular, ~~release~~ the release rate profile of leuprolide and efficacy, ~~i.e.~~ i.e., testosterone suppression, were determined by measuring the blood serum or plasma concentrations of leuprolide and testosterone as a function of time, as illustrated in Figure 18.

[00187] on p. 74 of the spec.

Please replace paragraph number ~~[0195]~~ with the following rewritten paragraph:

Example 25

~~*InVivo*~~*In Vivo* Release Rate Profiles and Efficacy of

Various Leuprolide Acetate Depot Formulations

[0195] A representative number of implantable gels as tabulated in Table 12 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles and efficacy as measured by testosterone suppression as described in Example 23 above. In particular, ~~release~~ the release rate profile of leuprolide and efficacy, ~~i.e.~~ i.e., testosterone suppression, were determined by measuring the blood serum or plasma concentrations of leuprolide and testosterone as a function of time, as illustrated in Figure 20.

[00188] on p. 74 of the spec.

Please replace paragraph number ~~[0196]~~ with the following rewritten paragraph:

[0196] In particular, Figure 20 illustrates representative *in vivo* sustained release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing P(DL)LA in either benzyl benzoate (BB) or benzyl alcohol (BA) for 6 months (formulations 58 and 59). Figure 21 illustrates the testosterone profiles of the leuprolide acetate depot formulations (formulations 58 and 59) as compared to the placebos without